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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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FOLEY HOAG, LLP PATENT GROUP, WORLD TRADE CENTER WEST 155 SEAPORT BLVD BOSTON, MA 02110			EXAMINER LEAVITT, MARIA GOMEZ	
			ART UNIT 1633	PAPER NUMBER
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/681,627

**Applicant(s)**

JUNE, CARL H.

**Examiner**

MARIA LEAVITT

**Art Unit**

1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 01-21-2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1, 3, 7-15, 17-19 and 21-45 is/are pending in the application.
- 4a) Of the above claim(s) 10-14, 18, 21 and 23-45 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 3, 7-9, 15, 17, 19 and 22 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

***Detailed Action***

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Status of claims. Claims 1, 3, 7-15, 17-19 and 21-45 are currently pending. Claims 10-14, 18, 21 and 23-45 were previously withdrawn from consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claims. This application contains claims 10-14, 18, 21 and 23-45 drawn to an invention nonelected with traverse in the reply filed on 10-30-2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01
3. Therefore, claims 1, 3, 7-9, 15, 17, 19 and 22 are currently under examination to which the following grounds of rejection are applicable.

***Rejections/objections maintained in response to Applicants' arguments or amendments:***

***Claim Rejections - 35 USC § 102(e)***

To the extent that the claimed invention embraces methods for inhibiting T cell activation comprising contacting the T cells with a phosphatidylinositol 3-kinase (PI3K) inhibitor that inhibits PI3K in the T cell, the following rejection applies.

Claims 1, 3 and 22 remain rejected under 35 U.S.C. 102(e) as being anticipated by Bonjouklian et al., (U.S. Patent No. 5,504,103, Date of Publication, April 2 1996).

***Response to Applicant Arguments as they apply to rejection of Claims 1, 3 and 22 under 35 U.S.C. 35 U.S.C. 102(e)***

At pages 6-7 of remarks, Applicants essentially argue that Bonjouklian does not disclose inhibiting phosphatidylinositol 3-kinase with wortmannin itself but with wortmannin analogs including 17 $\beta$ -hydroxy-wortmannin, 11-desacetoxywortmannin and compounds as illustrated by formula I, which are derived from wortmannin of formula II. Thus Applicants allege that the disclosure of Bonjouklian is only directed to compounds represented by formula I as further evidenced by the recitation of a compound of formula I in the claims. Furthermore, Applicants argue that the Examiner has incorrectly used hindsight reconstruction in formulating the rejection as the expression of PI3K by T cells was not known at the time of Bonjouklian, and that the contacting of CD28+ T cells with wortmannin resulting in inhibition of PI3K is novel. Such is not persuasive.

At the outset the examiner notes that claim 1 is broadly drawn to any agent that inhibits PI3K and claim 2 embraces any derivatives or analogs of wortmannin. As such the disclosure of 17 $\beta$ -hydroxywortmannin or one 17 $\beta$ -hydroxywortmannin analog taught by Bonjouklian reads on the claimed invention. In addition, Bonjouklian discloses that the claimed wortmannin analogs are derived from wortmannin to selectively inhibit PI3-kinase activity. In contrast, other PI3K inhibitors such as quercetin and certain analogs inhibit PI 3-kinase in addition to other kinases such as protein kinase C and PI 4-kinase (col. 2, lines 20-25). Thus the preferential disclosure of compounds of formula I as inhibitors of PI3K in Bonjouklian does not preclude the skilled artisan from having a reasonable expectation of success using wortmannin as an inhibitor of PI3K. Indeed, at the time the invention was made, it was well known in the art that wortmannin

was a potent inhibitor of phosphatidylinositol 3-kinase (Arcaro et al., 1993, Biochem J. 1993 December 1; 296(Pt 2): 297–301). It is noted that case law states that anticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure. In re Donohue, 766 F.2d 531, 533 [226 USPQ 619] (Fed. Cir. 1985). A reference may enable one of skill in the art to make and use a compound even if the author or inventor did not actually make or reduce to practice that subject matter. Bristol-Myers, 246 F.3d at 1379; see also In re Donohue, 766 F.2d at 533.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). As stated in the office action of 12-12-2008, Bonjouklian et al., does not specifically teach contacting T cells. However, T cells are abundantly present in mammals and inherently express phosphatidylinositol 3-kinase. Furthermore, the inhibition of phosphatidylinositol 3-kinase in T cells necessarily and inherently results in a change in cellular activities dependant on phosphatidylinositol 3-kinase, such as proliferation and lymphokine production (e.g., inhibition, activation).

***Claim Rejections - 35 USC § 112 - enablement***

To the extent that claims 1, 3, 7, 15, 17, 19 and 22 broadly embrace an *in vivo* method of treating a human subject suffering from an autoimmune condition comprising inducing

unresponsiveness to an antigen in a T cell wherein the antigen is an autoantigen so as to treat an inappropriate immune response against its own tissues, the following rejection applies.

Claims 1, 3, 7, 15-17, 19-20 and 22 remain rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for:

An *in vitro* method for inhibiting T cell activation as assessed by production of IL-2 comprising stimulating a T cell through the TCR/CD3 complex and CD28 and further contacting said T cell with an agent wherein the agent is selected from the group consisting of Wortmannin, quercetin and LY294002, thereby inhibiting the activity of phosphatidylinositol 3-kinase within the T cell,

does not reasonably provide enablement for claims directed to a method of inducing unresponsiveness to an antigen in a T cell with the intended use of treating a human subject suffering from an autoimmune disease.

***Response to Applicant Arguments as they apply to rejection of Claims 1, 3, 7, 15-17, 19-20 and 22 under 35 U.S.C. 112, first paragraph***

At pages 7 and 8 of remarks, Applicants essentially argue that sufficient disclosure is provided for the treatment of inflammatory and autoimmune disorders of different etiologies and therapeutic end points because one of ordinary skill in the art would appreciate that is desirable in all autoimmune disorders to downmodulate an immune response ( i.e., to inhibit T cell activation in a subject suffering from any autoimmune disorder). Moreover, Applicants allege that *de novo* determination of an effective target site would not be required as the target site of the invention is inhibition of T cell activation and production of IL-2 by the T cell, and effective

modes of delivery are routine experimentation as disclosed in the specification at page 8, lines 4-6; page 9, lines 14-31 and pages 11, lines 25 to page 12, line 7. Such is not persuasive.

As stated in the previous office action, the instant claims broadly embrace treatment for a genus of autoimmune diseases in a subject including type 1 diabetes, systemic lupus erythematosus, autoimmune encephalomyelitis, Crohn's, Multiple sclerosis and others. There is nothing in the specification teaching that inhibition of T cell activation can affect autoimmune disorders regardless of the etiology of the disease. The skilled artisan must extend the teachings of the specifications, such that an autoimmune disorder can be cured regardless of whether the disease results from a virally triggered autoimmune response, drug reaction, environmental factors and genetics among others. As each of these diseases is likely to have its own set of obstacles to effectively cure the resulting damage, the skilled artisan is left to address each of these obstacles without any guidance from the inventor as to how to proceed. How can such a broadly claimed evaluation step be performed without an undue experimentation when there is no supporting evidence to substantiate a reasonable correlation between inhibiting T cell activation and thus production of IL-2 by the T cell and any autoimmune disease? How could down modulation of an immune response in a subject suffering, for example, from both an autoimmune disorder and cancer or an infections disease requiring to boost the host's immune response towards cancer/microbial antigens be beneficial for said subject? The complex pathogenesis of autoimmune diseases is further reflected in the variable response of patients to immunomodulatory therapy and the lack of an effective unique treatment. Post filing art of Sykes et al. (Nature 2005, pp. 620-627), brings similar insight into lack of predictability in the art when he states, "although the prevention of autoimmunity might some day be clinical feasible, at the

moment we cannot predict such a diseases accurately enough to justify the use of toxic preventive treatment. Unfortunately, animal studies show that preventing the onset of autoimmunity is much easier than reversing established disease” (p. 620, col. 2, paragraph 3)”. Thus, the skilled artisan could not practice the claimed invention commensurate with the scope of the claims without first engaging in trial and error experimentation to identify the methods steps that must be added to those set forth in the claims of inhibiting T cell activation and production of IL-2 by the T cell in order to treat or cure a subject suffering from an autoimmune disorder as broadly claimed. Furthermore, the mere contemplation of the claimed genus of autoimmune disorders to be treated in the specification is not sufficient to support the present claimed invention directed to contacting the T cell with an agent inhibiting phosphatidylinositol 3-kinase within the T cell for the treatment of an autoimmune disorder in a subject.

***Rejection, Obviousness Type Double Patenting-***

Claims 1, 3 and 7-9 remain rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 7-10 of U.S. Patent No. 6, 632, 789 for the reasons already of record as set forth in the office action of 12-12-2008.

Applicants have not properly address the specific grounds for rejection as discussed in the previous office action setting.

***Other art for comment***

The following are cited to complete the record.

Arcaro et al., Wortmannin is a potent phosphatidylinositol 3-kinase inhibitor: the role of phosphatidylinositol 3,4,5-trisphosphate in neutrophil responses. Biochem J. 1993 December 1; 296(Pt 2): 297-301.

***Conclusion***

Claims 1, 3, 7-9, 15, 17, 19 and 22 are rejected.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

/Maria Leavitt/

Maria Leavitt, PhD  
Examiner, Art Unit 1633